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09/521,264	03/08/2000	Ernest V. Groman	1275/190	1949

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EXAMINER
WELLS, LAUREN Q

ART UNIT	PAPER NUMBER
1617	

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14

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 07-01)

Office Action Summary	Application No.	Applicant(s)	
	09/521,264	GROMAN ET AL.	
	Examiner	Art Unit	
	Lauren Q Wells	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 April 2002 and 04 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13,18-29,35,36 and 39-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13,18-29,35,36 and 39-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-13, 18-29, 35-36, 39-66 are pending. The Amendment filed 4/25/02, amended claims 35-36, 45, 57 and 59.

Request for Continued Examination

The request filed on 4/25/02 for Continued Examination (RCE) under 37 CFR 1.114 based on parent Application No. 09/521264 is acceptable and an RCE has been established. An action on the RCE follows.

Response to Arguments

Applicant's arguments with respect to claims 1-56 have been considered but are moot in view of the new ground(s) of rejection.

The Amendments filed 4/25/02, Paper No. 11, and 6/4/02, Paper No. 13, are sufficient to overcome the new matter objection in the previous Office Action, to the specification regarding pg. 1, lines 25-26 of the specification.

Specification

The amendments filed 4/25/02, Paper No. 11 and 6/4/02, Paper No. 13, are objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: the addition of the phrase "The term "derivatizing" and related terms (e.g. derivatives, derivatized, derivatization, etc) refer to the conventional sense of functionalization at the reactive sites of the composition".

The objection to new matter over pg. 17, lines 20-21, pg. 19, lines 22-23, and pg. 45, line 22, in the previous Office Action, Paper No. 7, is maintained. While Applicant has argued that

the specification has support for the matter, the Examiner does not find the support persuasive, as the specification did not originally recite "at higher doses", "at doses of vast excess", and "The dose administered in these studies was, as above, 100 mg test substance/kg body weight".

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5, 10-12,18-20, 21, 29, 35-36, 41, 45-47, 53, 57-60, 63-66 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(i) The term "derivatized" in claims 5 (line 3), 10 (line 1), 11 (line 1), 12 (line 1), 21 (line 2), 35 (lines 4-6), 64 (line 1), 65 (line 1), 66 (line 1) is still vague and indefinite, as the metes and bounds of this claim are unascertainable. It is not clear what compounds are encompassed by these claims. Applicant argues, "functionalization to produce derivatives occurs at the most reactive site on a molecule, the site termed the functional group". This argument is not persuasive, as this definition is not definite. This definition still comprises an endless possibility of chemical compounds.

(ii) The term "stable" in claims 18 (line 1), 19 (line 2) 20 (line 2), 64 (line 1) is a relative term which renders the claims indefinite. The term "stable" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. What is the criterion by which stable is measured? What differentiates stable versus not stable?

(iii) The phrase "carboxymethylated reduced coated ultrasmall superparamagnetic iron oxide colloid" in claim 53 (lines 3-4) is vague and indefinite, as it is not clear if the iron oxide colloid is carboxymethylated and reduced or if the coating is carboxymethylated and reduced.

(iv) Claim 29 (line 3) recites the limitation "wherein said complex remains a colloidal suspension". There is insufficient antecedent basis for this limitation in the claim, as none of the claims from which it depends, recites a colloidal suspension.

(v) The term "substantial" in claim 19 (line 4) is vague and indefinite, as it is not clear how substantial aggregation is measured or defined. What is unsubstantial aggregation? What differentiates substantial aggregation from unsubstantial aggregation?

(vi) Claim 35 is vague and indefinite, as it is confusing. First, the phrase "administering. . .a polysaccharide of the type wherein there is a risk of edematous response" is confusing. The term "type" is not a positive recitation. Thus, it is not clear what method is actually being claimed. What is a "risk of an edematous response"? What defines or characterizes this? What does "utilizing for administration a derivatized reduced polysaccharide composition" mean? Is the composition actually being administered? What is "utilizing" a composition? Quantitatively, what is "an extent of derivatization sufficient to produce an edematous response? Specifically, what differentials "sufficient" from "insufficient" and what denotes a "edematous response"? Quantitatively, what is "decreased in comparison to that resulting from utilizing a polysaccharide that has not been thus derivatized"?

(vii) Claims 36 and 45 are vague and indefinite for the reasons that are similarly discussed in part (vi) of this 112 rejection. Furthermore, regarding claim 36, the phrase "utilizing for administration carboxymethylated reduced dextran in lieu of dextran" is confusing.

In lieu of dextran where? And regarding claim 45, what is a "polysaccharide-derived iron oxide"? How can an iron oxide be derived from a polysaccharide?

(viii) The term "decreased" in claim 41 (line 2) is a relative term which renders the claim indefinite. The term "decreased" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. What is the criterion by which decreased is measured? What differentiates decreased versus increased or steady?

(ix) Claim 46 is vague and indefinite, as it is confusing. How can merely administering an effective amount of a composition result in an MRI? Is there not a step missing between administering the composition and obtaining the image? Furthermore, what does it mean to "obtain an MRI". Does it mean to visualize it? The phrase "followed within a single clinical visit by administering a further effective does, to obtain a further MRI" is not understood. What is being followed? The method steps of this claim are not clear.

(x) Claim 57 is vague and indefinite, as it is confusing. The term "type" is not a positive recitation. Thus, it is not clear what method is actually being claimed. Also, what does it mean to "obtain" a composition? Does it mean to make the composition? What is a "risk of an edematous response"? What defines this or characterizes this? Quantitatively, what is "an extent of carboxyalkylation sufficient to produce an edematous response? Specifically, what differentials "sufficient" from "insufficient" and what denotes an "edematous response"? Furthermore, what composition is being claimed? Deriving a composition from a polysaccharide could result in millions or billions of possible compositions. Lastly, what is "sufficient to

produce decreased edematous response of the derived composition"? Quantitatively, what does this refer to? What is the means of comparison between sufficient and insufficient?

(xi) Claims 57-59 provide for the use of a pharmaceutical composition, but, since the claim does not set forth any steps involved in the method/process for a pharmaceutical composition, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 57-59 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

(xii) Claim 59 is vague and indefinite for the reasons that are discussed in parts (x) and (xi) of this 112 rejection.

(xiii) Claim 60 recites the limitation "after the reacting step" in line 1. There is insufficient antecedent basis for this limitation in the claim.

(xiv) Claim 63 provides for the use of a product, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 63 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e.,

results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

(xv) The term "such polysaccharide" in claims 65 and 66 (lines 2) is vague and indefinite, as it is not clear if this term refers to the "reduced derivatized polysaccharide" in line 1 of the claims, or if this term refers to another polysaccharide.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-13, 18-29, 35, 36, 29-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Maruno et al. (6,165,378) in view of Golman et al. (5,985,245) in further view of Lewis et al. (5,055,288).

Maruno et al. ('378) teach a polysaccharide-magnetic metal oxide complex consisting of a polysaccharide derivative obtained by carboxyalkyl-etherifying a polysaccharide, for use in MRI. Polysaccharides disclosed include dextran and carboxyalkyl-ethers disclosed include carboxymethyl ether, carboxyethyl ether, and carboxypropyl ether. The polysaccharides are reduced and obtained by subjecting the polysaccharide to a)a method using hydrogen gas in the presence of palladium carbon; or b) a method using sodium boronhydride. Metal oxides disclosed include iron oxides. A salt form of the complex is disclosed. The complex is made by

combining the iron oxide and polysaccharide and heating them from room temperature to 120 C for 10 minutes to 10 hours. The complex can be superparamagnetic and can be administered in the form of an aqueous sol. The effective dose of the complex is different, depending on the specific purposes of the complex. A broad range of 1umol/kg-10mmol/kg is disclosed. Parenteral injection, infusion, direct enteric administration, and oral administration are methods of administration. The reference lacks sterilization by autoclaving and kits. See Col. 1, line 44-Col. 2, line 45; Col. 5, line 37-Col. 22, line 15.

Lewis et al. teach a vascular magnetic imaging method and an agent comprising biodegradable superparamagnetic metal oxides. The agents are as disclosed as being autoclaved. Iron is disclosed as a superparamagnetic oxide and dextran is disclosed as a macromolecular species associated with the iron oxide. See Col. 3, line 15-Col. 9, line 35; Col. 11, line 64-Col. 16, line 31.

Golman et al. teach contrast agents for MRI using a manganese compound and kojic acid. Negative contrast agents disclosed for use in the composition superparamagnetic species, such as iron oxide bound with polysaccharides. A multiple container contrast agent kit is disclosed. See Col. 3, line 40-Col. 5, line 18.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the filtration step of Maruno with the autoclaving step of Lewis et al. because a) Maruno et al. and Lewis et al. are both directed toward MRI contrast agents comprising superparamagnetic dextran-iron oxide complexes; b) Maruno et al. teach sterilization via filtration, and Lewis et al. teach autoclaving, filtration, irradiation, and chemical treatment as interchangeable sterilization techniques; c) Lewis et al. teach that autoclaving is the preferred

technique for sterilization since the bottle or container need not be sterile prior to fill and furthermore teach that while filtration is an alternative, that superparamagnetic fluids, such as dextran-iron oxide complexes, filter poorly at high concentrations.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to add the kit of Golman et al. to the invention of the combined references because a) Golman et al. and the combined references all teach supraparamagnetic iron oxides bound to polysaccharides as contrast agents for use as MRI contrast agents, and Golman et al. teach that it is known to utilize kits for such contrast agents.

Unexpected Results

It is applicant's burden to demonstrate unexpected results over the closest prior art. See MPEP 716.02, also 716.02 (a) - (g). Furthermore, the unexpected results should be demonstrated with evidence that the differences in results are in fact unexpected and unobvious and of both statistical and practical significance. *Ex parte Gelles*, 22 USPQ2d 1318, 1319 (Bd. Pat. App. & Inter. 1992). Moreover, evidence as to any unexpected benefits must be "clear and convincing" *In re Lohr*, 137 USPQ 548 (CCPA 1963), and be of a scope reasonably commensurate with the scope of the subject matter claimed, *In re Linder*, 173 USPQ 356 (CCPA 1972).

In the instant case, Applicant's declaration filed 4/25/02 is not sufficient, as it provides not objective data and no ***unexpected*** results. While Applicant argues that his invention is distinguished over the prior art because of its unique ability to be autoclaved, the Application has provided no objective data and has not shown how this is unexpected over the teachings of the prior art.

The Examiner furthermore respectfully points out the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lauren Q Wells whose telephone number is (703) 305-1878. The examiner can normally be reached on M-F (7-5:30), with alternate Mondays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Minna Moezie can be reached on (703) 308-4612. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1234.

lqw
July 1, 2002

RUSSELL TRAVERS
PRIMARY EXAMINER
GROUP 1200